REMARKS

Status of the Claims.

Claims 1-4, 6-10, 20-29, 31 and 32 are pending with entry of this amendment, claims 5, 11-19, and 30 having been cancelled and claim 32 having been added.

35 U.S.C. §112, First Paragraph.

The rejection of claims 1-4, 6-10, 20-29, and 31 under 35 U.S.C. §112, first paragraph was maintained. The Examiner alleged that the specification is not enabling for a method of increasing the efficacy of a gastric H+/K+-ATPase inhibitor (PPI) in a human in need of a PPI by administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin, a gastrin, or a gastrin analogue in conjunction with the PPI" . . . "**because the specification discloses cursory conclusions without data supporting the findings . . .**". Applicants traverse.

Make and Use Enablement

The specification clearly teaches one of skill how to administer a pentagastrin, or a gastrin, in conjunction with said gastric proton pump inhibitor as recited in the claims. Proton pump inhibitors **(PPIs) are well known to those of skill in the art, are routinely administered to humans** (*see, e.g.,* Omeprazole (brand names: Losec®, Prilosec®), Lansoprazole (brand names: Prevacid®, Zoton®, Inhibitol®), Esomeprazole (brand names: Nexium®), Pantoprazole (brand names: Protonix®, Somac®, Pantoloc®), and Rabeprazole (brand names: Rabecid®, Aciphex®, Pariet®). Similarly, **both gastrin and pentagastrin have been administered to various animals and humans**, *e.g.* as a model system (*see, e.g.*, Example 1) and **tolerances of humans for gastrin and pentagastrin are well known to those of skill in the art**. The art thus recognizes standard modes of administration of both PPIs and gastrin/pentagastrin.

Operability.

Since Applicants have clearly enabled the administration of a PPI in conjunction with a gastrin or pentagastrin, The Examiner's rejection under §112, is really based on the allegation that Applicants haven't provided data supporting the operability of the claimed invention. In effect, the

Examiner alleges that Applicants haven't shown that the invention works as claims and because operability allegedly hasn't been established the claimed invention is not enabled.

This rejection is properly made under both 35 U.S.C. §112/§101, first paragraph (*see, e.g.,* M.P.E.P. §2107.01 (IV), *In re Ziegler,* 992 F.2d 1197, 1200-1201, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993), *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); and the like).

Contrary to the Examiner's assertion, **it is well accepted law, however, that a post-filing reference can be used to support the operability of a claimed method.** Additional evidence of operability is provided as discussed below:

Declaration under 37 C.F.R. §1.132

Additional evidence of the operability of the claimed invention is provided herewith in the accompanying Declaration under 37 C.F.R. §1.132. The Declaration discloses experiments in a standard mouse model that unambiguously show that gastrin enhances the activity of a PPI (compare upper curve with lower curve in Figure 1). **Moreover, the enhanced activity is produced by injected gastrin.**

Barda *et al.*

As explained in a previous response, Barda *et al.* (2004) *Supplement to Gastroenterology*, 12(4): Suppl. 2, Abstract M1439 states:

> These data indicate that **prestimulation of gastric proton pumps with oral PG [pentagastrin] enhances the inhibitory effect of omeprazole** [a PPI] on acid secretion. This effect is mediated by a local effect of PG. **Co-administraton of PG and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole**. [emphasis added]

Applicants have thus provided data showing that both oral and injected gastrin and/or pentagastrin can be effective to enhance the activity of a PPI. Applicants have thus shown that the claimed invention is fully operable.

The Examiner has failed to provide any objective evidence to refute Barda *et al.* Specifically the Examiner has offered no objective basis to establish why the pentagastrin/omeprazole

combination is not predictive for the combination of gastrin or pentagastrin and any other PPI. Similarly the Examiner has offered no objective basis to establish why the rat or mouse model is not a good model for behavior of these agents in humans. Accordingly the Examiner has failed to refute Applicants' evidence and the rejection under 35 U.S.C. §112, first paragraph/35 U.S.C. §101(a) should be withdrawn.

In this regard, the Examiner is also reminded that the Federal Circuit expressly states:

> The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second state of testing, by which he apparently means ***in vivo* testing in humans** and therefore **are not reasonably predictive of the succss of the claimed compounds for treating cancer in humans**. The Commissioner, as did the Board, **confuses the requirement sunder the law for obtaining a patent with the requiremens for obtaining government approval to market a particular drug for human consumption**. . .
>
> Our court's predecessor has determined that **proof of an alleged pharmaceutical property of a compound by statistically significant tests with standard experimental animal is sufficient to establish utility**.

Similarly, the M.P.E.P. §2107.02(c) states that:

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing an animal model or a combination thereof **almost invariably** will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process. [emphasis added].

The cited reference and the accompanying Declaration thus clearly and unambiguously supports the efficacy of the claimed method. The Examiner has offered no objective basis to establish that the standard rat model described in Barda *et al.* is not reasonably correlated with the therapeutic operability/utility of the presently claimed invention. Accordingly the Examiner has failed to meet her burden and the rejection under 35 U.S.C. §112, first paragraph, (really 35 U.S.C. §101(a)/§112) should be withdrawn.

Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4161.

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Respectfully submitted,

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